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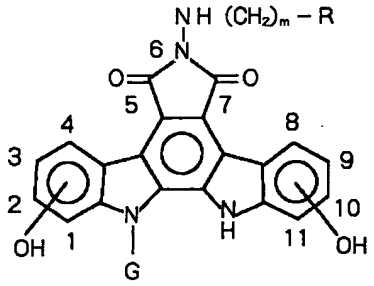
(54) 【Title of Invention】 Antitumor Indolopyrrolocarbazole Derivatives

(57) 【Abstract】
【Problem】 Creation of Novel Antitumor Agents
【Solution Means】
A compound represented by the following general formula or a pharmaceutically acceptable salt thereof
【Com. 1】



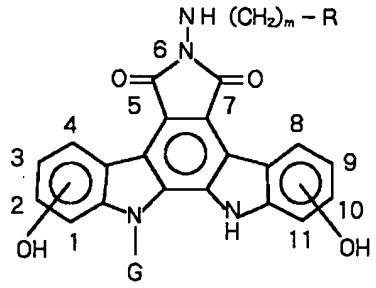
[I]

wherein R represents a phenyl, naphthyl, pyridyl, furyl or thienyl group each of which has one or more substituents selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group except that when the phenyl, naphthyl, pyridyl, furyl or thienyl group has a lower alkoxy group as a substituent, each of which simultaneously has another substituent selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group, m represents an integer of 1 to 3, and G represents a β-D-glucopyranosyl group, and the positions of substitution of the hydroxyl groups on the indolopyrrolocarbazole ring are the 1- and 11-positions, or the 2- and 10-positions.

【Scope of Claims】

【Claim 1】 A compound represented by the general formula or a pharmaceutically acceptable salt thereof

【Com. 1】



[I]

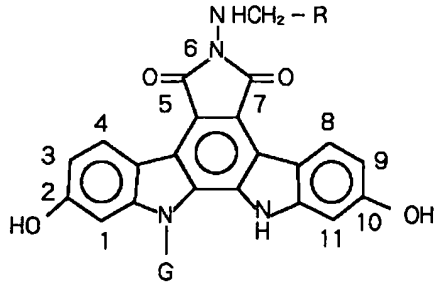
wherein R represents a pheny, naphthyl, pyridyl, furyl or thienyl group each of which has one or more substituents selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group except that when the pheny, naphthyl, pyridyl, furyl or thienyl group has a lower alkoxy group as a substituent, each of which simultaneously has another substituent selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group,

m represents an integer of 1 to 3, and

G represents a β-D-glucopyranosyl group, and the positions of substitution of the hydroxyl groups on the indolopyrrolocarbazole ring are the 1- and 11-positions, or the 2- and 10-positions.

【Claim 2】 The compound represented by the following general formula or the pharmaceutically acceptable salt thereof, according to claim 1

【Com. 2】

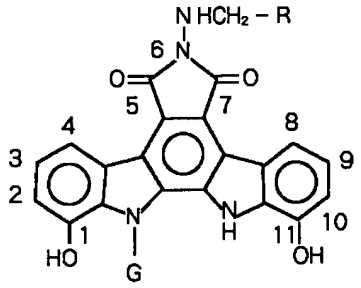


[I－a]

wherein R, m and G are as defined in claim 1.

【Claim 3】 The compound represented by the following general formula or the pharmaceutically acceptable salt thereof, according to claim 1

【Com. 3】



[I – b]

wherein R, m and G are as defined in claim 1.

【Claim 4】 An antitumor agent containing a compound or pharmaceutically acceptable salt thereof according to claim 1,2 or 3.

【Detailed Description of the Invention】

【0001】

【Industrially Applicable Field】

This invention is useful in the pharmaceutical field, and, more detailedly, relates to novel indolopyrrolocarbazole derivatives inhibiting growth of tumor cells and exerting antitumor effect, processes for preparation thereof and their use.

【0002】

【Prior Art】

Many compounds are already put to practical use as pharmaceuticals in the field of tumor chemotherapy. However, their effects are not always sufficient against various kinds of tumors, and the problem of resistance of tumor cells to these drugs also makes the methods of clinical use complicate (see, Proceedings of the 47th Annual Meeting of Japan Cancer Society, pages 12-15, 1988).

【0003】

Under the circumstances, development of novel anticancer substances is always desired in the field of cancer treatment. Particularly, there is need for substances overcoming resistance to existing carcinostatic substances and showing effectiveness against cancers on which existing carcinostatic substances cannot exert sufficient effect.

【0004】

Under these present circumstances, the present inventors have widely screened metabolites of microorganisms, and as a result, they found a novel compound BE-13793C (12,13-dihydro-1,11-dihydroxy-5H-indolo[2.3-a]pyrrolo[3,4-c]carbazole-5,7 (6H) -dione) having antitumor activity (see, EP-A2-0388956).

【0005】

Thereafter, they have tried to create compounds having further excellent antitumor activity by chemically modifying BE-13793C, and disclosed such compounds in prior patent applications (EP-A1-0528030, EP-A1-0545195, WO95/30682 and WO96/04293).

【0006】

【Problems to be Solved by the Invention】

It is a problem to be solved in the present invention to create compounds having further excellent antitumor activity by chemically modifying indolopyrrolocarbazole antitumor substances disclosed in the prior patent applications.

【0007】

【Means for Solving the Problems】

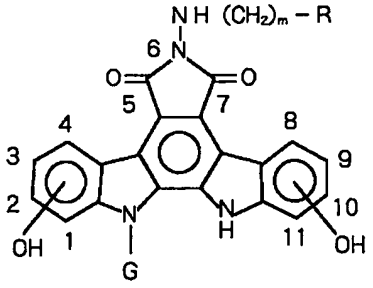
For solving the above problem, the present inventors have synthesized a wide range of indolopyrrolocarbazole derivatives and examined their antitumor activity, and found that compounds represented by the later-described general formula [I] show further excellent antitumor activity than the indolopyrrolocarbazole compounds disclosed in the prior applications, and completed the present invention.

【0008】

Namely, the invention relates to a compound represented by the general formula or a pharmaceutically acceptable salt thereof, and a use thereof:

【0009】

【Com. 4】



[I]

wherein R represents a phenyl, pyridyl, furyl or thienyl group each of which has one or more substituents selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group except that when the phenyl, pyridyl, furyl or thienyl group has a lower alkoxy group as a substituent, each of which simultaneously has another substituent selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group, m represents an integer of 1 to 3, and G represents a β-D-glucopyranosyl group, and the positions of substitution of the hydroxyl groups on the indolopyrrolocarbazole ring are the 1- and 11-positions, or the 2- and 10-positions.

【0010】

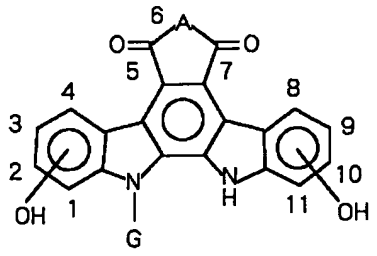
Description is made below on processes for preparing the compounds of the invention.

【0011】

An indolopyrrolocarbazole derivative of the invention can be prepared by reacting a compound represented by the general formula

【0012】

【Com. 5】



[II]

wherein, A represents NH or H, and G is as defined above,
the compound being a known compound disclosed in EP-A1-0528030, EP-A1-0545195, WO95/30682 and WO96/04293, with a compound represented by the general formula

【0013】

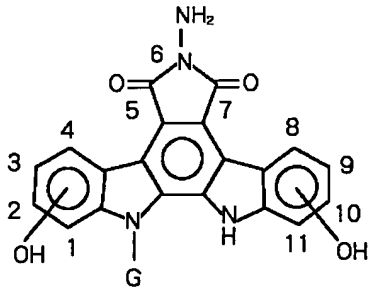
【Com. 6】

$$H_2N\text{-}NH(CH_2)_mR \qquad [III]$$

wherein, R and m are as defined above,
or by condensing a compound represented by the general formula

【0014】

【Com. 7】



[IV]

wherein, G is as defined above,
with a compound represented by the general formula

【0015】

【Com. 8】

$$R^1(CH_2)_mCHO \qquad [V]$$

wherein, R^1 has the same meaning as R or means R wherein hydroxyl groups are protected, and m is as defined above,
then carrying out reduction, and, if necessary, removing the protective groups,
or by reacting a compound of the general formula [IV] with a compound represented by the general formula

【0016】

【Com. 9】

$R^1(CH_2)_mL$ [VI]

wherein, L means a leaving group, and R^1 and m are as defined above, , and, if necessary, removing the protective groups.

【0017】

The reaction between the compound represented by the general formula [II] and the compound represented by the general formula [III] is reaction between an imide or an acid anhydride and a hydrazine derivative, well-known in the chemical field. This reaction can be carried out using a solvent usually having no bad influenece on the reaction, such as, for example, tetrahydrofuran or N,N-dimethylformamide. The use amount of the compound [III] is usually a little excess to 5 molar equivalents based on the compound [II], but a largely excess use of the former is possible.

【0018】

The reaction temperature is usually in the range of -50℃ to the boiling point of the solvent, but, if necessary, temperature higher than or lower than the temperature can be used. The reaction time is usually in the range of 30 minutes to 2 days, but time longer than or shorter than the time can be used.

【0019】

The reaction of preparing a compound [I] by condensing a compound represented by the general formula [IV] with a compound represented by the general formula [V] and then carrying out reduction can be carried out in the same reaction system, but in some occasion, it is also possible to once isolate the Schiff base as an intermediate product. Namely usually, the reaction can be carried out by mixing the compound [IV] with the compound [V] in a suitable solvent and then adding a reducing agent. The reaction is preferably carried out in the presence of an acid such as acetic acid or hydrochloric acid. As usable solvents, there can, for example, be mentioned alcoholic solvents such as methanol and ethanol, aprotic polar solvents such as N,N-dimethylformamide, etc. The reduction of the Schiff base can be carried out using a metal hydride complex such as sodium cyanoborohydride, or the like, and also by catalytic reduction.

【0020】

The reaction between a compound of the general formula [IV] and a compound of the general formula [VI] is alkylation reaction of an amine, and can be carried out by a known method, for example by reaction with an alkyl halide, alkyl mesylate or alkyl tosylate or the like.

【0021】

The products of the above reactions can be purified by methods known in the field of organic chemistry, for example by precipitation methods, solvent extraction methods, recrystallization, chromatography, etc.

【0022】

Further in the invention, pharmaceutically acceptable salts of compounds obtained by the above processes are included. As such salts, there can be mentioned salts with an alkali metal such as for example potassium or sodium, salts with an alkaline earth metal such as for example calcium, salts with a basic organic compound such as for example ethylamine or arginine, salts with an inorganic acid such as hydrochloric acid or sulfuric acid, and salts with an organic acid such as acetic acid, citric acid or maleic acid.

【0023】

The compounds of the invention represented by the formula [I] show excellent antitumor action.

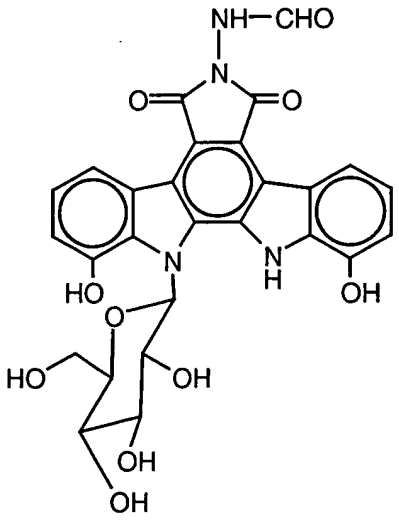
【0024】

Effect on human gastric cancer MX-1

MX-1 solid tumor previously subcutaneously implanted in a nude mouse and grown was thinly cut, and its cubes with each side 3 mm were subcutaneously implanted in test mice. After the implantation, starting from the time when the tumor grew into 0.3 cm^3, various dosages of a test compound were injected once a day for 5 consecutive days into the tail veins of the mice. The same injections were then made for further 5 days after 2 days of interval (treatment schedule: 5/w×2) or once every 3-4 days, four times (treatment schedule: 2/w×2). 20 days or 32 days after the start of the treatment, the length (L) and the breadth (W) of each of the tumors were measured, and its volume (V) was calculated ($V=1/2\times L\times W^2$) . A tumor growth inhibition proportion was calculated based on the volume, and a total dose to inhibit tumor growth by 75 % (GID_{75}, mg/kg) was then determined. As a control compound, a compound represented by the following formula was used. The results are shown in Table 1.

【0025】

【Com. 10】



【0026】

【Table 1】

Table 1 Effect of Compounds of the Invention on human gastric cancer MX-1

Test Compound	Treatment Schedule	GID_{75} (mg/kg total)
Example 3	2/w×2	<90
Example 5	5/w×2	<90
Example 10	5/w×2	<90
Example 12	2/w×2	97
Example 14	2/w×2	<12
Example 27	2/w×2	<4.5
Example 28	2/w×2	<36
Example 30	5/w×2	16

Example 31	5/w×2	<30
Example 33	5/w×2	<30
Example 35	5/w×2	82
Example 36	5/w×2	<30
Example 37	5/w×2	32
Example 38	5/w×2	19
Example 39	2/w×2	<30
Control compound	5/w×2	1900

Compounds provided by the present invention show a much better antitumor action than the control compounds, as shown in the above pharmacological test results.

【0027】

As apparent from the results of the above pharmacological tests, the compounds of the invention show an excellent antitumor action, and are useful as antitumor agents for prophylaxis and/or treatment of diseases, especially for treatment of cancers. As administration forms in use as antitumor agents of the compounds of the invention, various forms can be selected, and there can be mentioned peroral agents such as for example tablets, capsules, powders, granules and liquids, or sterilized liquid parenteral agents such as for example solutions and suspensions.

【0028】

Solid preparations such as tablets, capsules, granules and powders can be prepared using compounds of the invention alone, but can also be prepared further using suitable additives. As the suitable additives, there can be mentioned conventional additives, for example, sugars such as for example lactose and glucose, starches such as for example corn, wheat and rice, fatty acids such as for example stearic acid, inorganic salts such as for example magnesium metasilicate aluminate and anhydrous calcium phosphate, synthetic macromolecules such as for example polyvinylpyrrolidone and polyalkylene glycols, fatty acid salts such as for example calcium stearate and magnesium stearate, alcohols such as for example stearyl alcohol and benzyl alcohol, synthetic cellulose derivatives such as for example methylcellulose, carboxymethylcellulose, ethylcellulose and hydroxypropylmethylcellulose, and further, water, gelatin, talc, vegetable oils, gum arabic, etc.

【0029】

These solid preparations such as tablets, capsules, granules and powders can contain, generally 0.1 to 100 % by weight, preferably 5 to 100 % by weight of an effective ingredient.

【0030】

Liquid preparations can be prepared as forms of suspensions, syrups, injections, etc. using suitable additives usually used in liquid preparations, such as water, alcohols or vegetable oils including soybean oil, peanut oil and sesame oil.

【0031】

Particularly, as solvents suitable in parenteral administration including intramuscular injection, intravenous injection and subcutaneous injection, there can for example be mentioned distilled water for injection, aqueous lidocaine hydrochloride solution (for intramuscular injection), physiological saline, aqueous glucose solution, ethanol, polyethylene glycol, liquids for intravenous injection (e.g., aqeous solutions of cetric acid and sodium citrate, etc.), electrolyte solutions (for intravenous injection by drip

and for intravenous injection), etc., or their mixed solutions.

【0032】

These injections may include not only those wherein previous dissolution is made, but also those in the form of dissolving powder alone or with suitable additives when used. These injections usually contain 0.1 to 10 % by weight, preferably 1 to 5 % of an effective ingredient.

【0033】

Liquid preparations such as suspensions and syrups for oral administration can contain 0.5 to 10 % by weight of an effective ingredient.

【0034】

It should be noted that the actually preferred dose of the compounds of the invention is varied depending on kinds of compounds used, kinds of compositions prepared, application frequency, particular sites to be treated, hosts and timors. For example, the dose of each compound per day and per one adult is 10 to 500 mg in the case of oral administration, and 10 to 100 mg in the case of parenteral administration, preferably intravenous injection. The frequency of administration is varied depending on administration methods and symptoms, but the administration can be made in a time or in devided 2 to 5 times. Administration methods including intermittent administration such as every two-days administration or every three-days administration can also be used.

【0035】

【Mode for Carrying out the Invention】

【0036】

【Example】

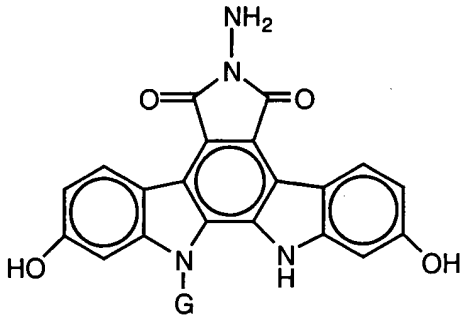
The invention is further specifically described below according to examples, but the invention is not limited to these examples.

【0037】

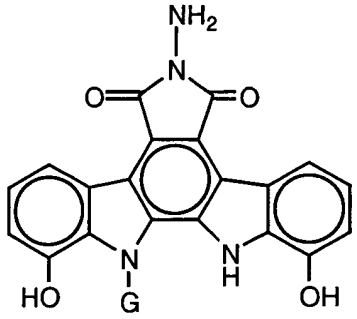
Compounds having the following structural formulae, which were used as starting compounds, are hereinafter referred to as follows.

【0038】

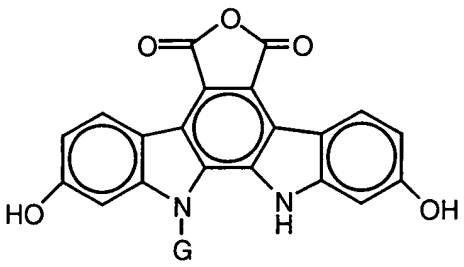
【Com. 11】



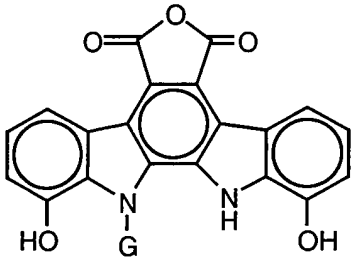
Compound A



Compound B



Compound C



Compound D

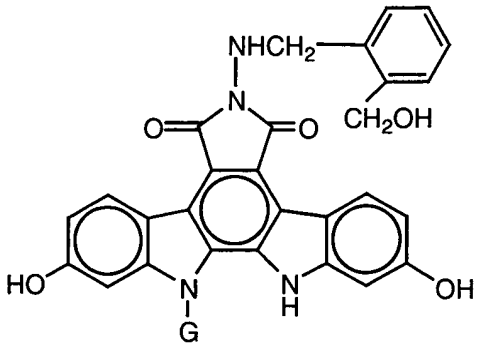
wherein, G represents a β-D-glucopyranosyl group, which is the same in the following examples.

Example 1

Compound represented by the structural formula

【0039】

【Com. 12】



【0040】

25 mg of Compound A and 90 mg of (2-t-butyldimethylsilyloxymethyl)benzyl bromide were dissolved in 1 ml of N,N-dimethylformamide, and the mixture was stirred overnight at room temperature. The resulting reaction mixture was concentrated to dryness, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated, and the concentrate was placed on a Sephadex LH-20 column for

chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was washed with chloroform to obtain 3.6 mg of the compound represented by the above formula.

FAB-MS(m/z):655$(M+H)^+$

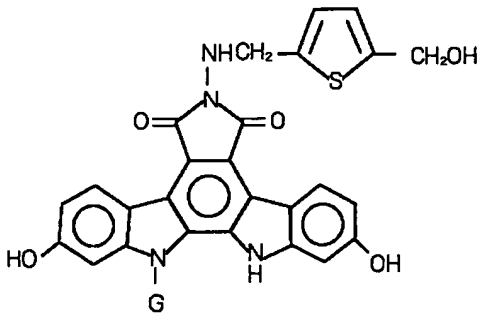
^{1}H-NMR(300MHz,DMSO-d_6,δp pm)11.19(1H,s),9.78(1H,s),9.75(1H,s),8.86(1H,d, J=8.6Hz),8.78(1H,d,J=8.2Hz),7.44(1H,d,J=7.2Hz),7.37(1H,d,J=7.6Hz),7.13-7.28(3H, m),6.98(1H,s),6.78-6.88(2H,m),5.95-6.05(2H,m),5.85(1H,br),5.33(1H,d,J=3.2Hz), 5.10-5.17(2H,m),4.92(1H,d,J=4.0Hz),4.28(2H,d,J=5.2Hz),3.72-4.10(4H,m),3.45-3.55 (2H,m)

Example 2

Compound represented by the structural formula

【0041】

【Com. 13】



30 mg of Compound A and 30 mg of (5-t-butyldimethylsilyloxymethylthiophene)-2-carboxyaldehyde were dissolved in 6 ml of methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80℃ for 4 hours. The reaction mixture was cooled to room temperature, 20 mg of sodium cyanoborohydride and 200 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 27 mg of the compound represented by the above formula.

Rf value: 0.37 (Kieselgel 60F_{254} made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

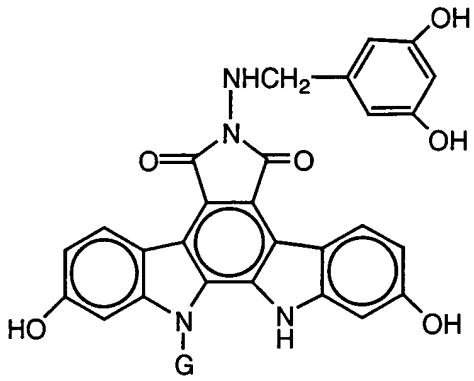
FAB-MS(m/z):660(M^+)

^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.19(1H,s),9.79(1H,s),9.75(1H,s),8.86(1H,d, J=9.3Hz),8.78(1H,d,J=9.0Hz),7.17(1H,d,J=2.1Hz),6.97(1H,d,J=2.1Hz),6.89(1H,d,J=3. 6Hz),6.82(1H,dd,J=2.1,9.3Hz),6.79(1H,dd,J=2.1,9.0Hz),6.73(1H,d,J=3.3Hz),6.10(1H,t ,J=4.5Hz),5.97(1H,d,J=8.1Hz),5.86(1H,t,J=3.3Hz),5.35(1H,t,J=6.0Hz),5.32(1H,d,J=4. 8Hz),5.12(1H,d,J=4.8Hz),4.92(1H,d,J=5.4Hz),4.52(2H,d,J=5.7Hz),4.40(2H,d,J=4.2Hz),4.02(1H,m),3.91(2H,m),3.78(1H,m),3.50(2H,m)

Example 3

Compound represented by the structural formula

【0042】
【Com. 14】



100 mg of Compound A and 131.2 mg of 3,5-dihydroxybenzaldehyde were dissolved in 10 ml of N,N-dimethylformamide, and the mixture was stirred at 80℃ for 48 hours. The reaction mixture was concentrated under reduced pressure, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 90.3 mg of an intermediate compound. 20 mg of this intermediate compound was suspended in 5 ml of methanol, 10 mg of sodium cyanoborohydride and several drops of a 10% solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. After distilling off methanol under reduced pressure, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline, dried and concentrated, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 18 mg of the compound represented by the above formula.

Rf value: 0.30 (Kieselgel 60F_{254} made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

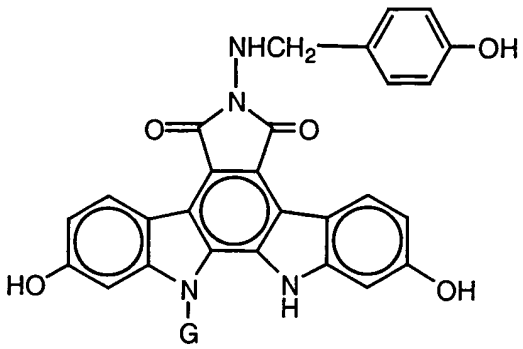
FAB-MS(m/z):657$(M+H)^+$

^{1}H-NMR(300MHz,DMSO-d_6,δp pm)11.19(1H,s),9.77(2H,br),9.11(2H,s),8.87(1H,d, J=8.6Hz),8.79(1H,d,J=8.6Hz),7.17(1H,s),6.97(1H,s),6.78-6.84(2H,m),6.34(2H,s), 6.06(1H,s),5.96(1H,d,J=8.3Hz),5.83-5.87(2H,m),5.34(1H,s),5.12(1H,s), 4.92(1H,d,J=3.9Hz),4.04(2H,d,J=4.5Hz),3.91-3.99(3H,m),3.75-3.88(1H,m),3.49(2H,s)

Example 4

Compound represented by the structural formula

【0043】
【Com. 15】



30 mg of Compound A and 14 mg of 4-hydroxybenzaldehyde were dissolved in 6 ml of methanol, 14 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was cooled to room temperature, 20 mg of sodium cyanoborohydride and 200 ml of a 10% solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 31 mg of the compound represented by the above formula.

Rf value: 0.41 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS(m/z):640(M^+)

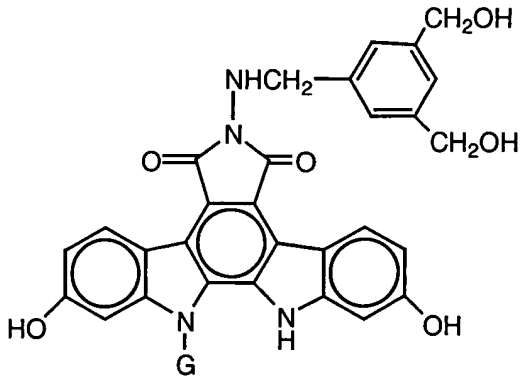
^{1}H-NMR(300MHz,DMSO-d_6,δp pm)11.17(1H,s),9.77(1H,s),9.74(1H,s),9.24(1H,s), 8.86(1H,d,J=8.4Hz),8.78(1H,d,J=8.4Hz),7.25(2H,d,J=8.7Hz),7.17(1H,d,J=1.8Hz),6.97 (1H,d,J=1.8Hz),6.83(1H,dd,J=1.8,8.7Hz),6.80(1H,dd,J=1.8,8.7Hz),6.67(2H,d,J=8.1Hz),5.96(1H,d,J=8.1Hz),5.87(1H,t,J=4.8Hz),5.85(1H,t,J=3.9Hz),5.32(1H,d,J=4.5Hz),5.10 (1H,d,J=5.1Hz),4.91(1H,d,J=4.8Hz),4.12(2H,m),4.03(1H,m),3.91(2H,s),3.78(1H,m),3. 50(2H,m)

Example 5

Compound represented by the structural formula

【0044】

【Com. 16】



30 mg of Compound A and 20 mg of 3,5-dihydroxymethylbenzaldehyde were dissolved in 6 ml of methanol, 20 ml of acetic acid was added, and the mixture was stirred at 80℃ for 3 hours. The reaction mixture was brought back to room temperature, 10 mg of sodium cyanoborohydride and several drops of a 10% solution of hydrochloric acid in methanol were added, and the mixture was stirred at room

temperature for 30 minutes. The reaction mixture was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 22 mg of the compound represented by the above formula.

Rf value: 0.35 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS(m/z):684 (M^+)

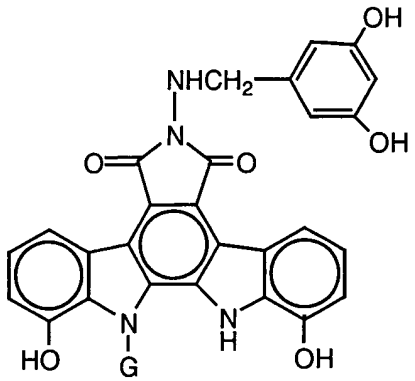
^{1}H-NMR(300MHz,DMSO-d_6,δp pm)11.19(1H,s),9.79(1H,s),9.76(1H,s),8.88(1H,d, J=8.7Hz),8.80(1H,d,J=8.7Hz),7.32(2H,s),7.18(2H,s),6.98(1H,d,J=1.8Hz),6.81(2H,dt,J =1.8,8.7Hz),5.97(1H,d,J=8.7Hz),5.93(1H,t,J=4.8Hz),5.87(1H,t,J=3.2Hz),5.34(1H,d,J= 4.2Hz),5.15(2H,t,J=6.3Hz),5.12(1H,d,J=4.8Hz),4.92(1H,d,J=4.8Hz),4.49(2H,s),4.47(2 H,s),4.22(2H,d,J=5.1Hz),4.03(1H,m),3.92(2H,s),3.78(1H,m),3.50(2H,m)

Example 6

Compound represented by the structural formula

【0045】

【Com. 17】



53 mg of Compound B and 69 mg of 3,5-dihydroxybenzaldehyde were dissolved in 3 ml of N,N-dimethylformamide, and the mixture was stirred overnight at 80℃. The reaction mixture was concentrated under reduced pressure, the concentrate was dissolved in 10 ml of methanol, an excess amount of sodium cyanoborohydride and 0.5 ml of a 10% solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, water was added, the mixture was extracted with a mixed solvent of ethyl acetate/methyl ethyl ketone, and the organic layer was washed with saturated saline, dried and concentrated. The residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 4.8 mg of the compound represented by the above formula.

Rf value: 0.2 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; chloroform:methanol=3:1)

FAB-MS(m/z):657$(M+H)^+$

^{1}H-NMR(300MHz,DMSO-d_6,δp pm)10.89(1H,s),10.33(1H,br),9.97(1H,br),9.11(1H, s),8.70(1H,d,J=6.8Hz),8.52(1H,d,J=7.7Hz),7.15-7.21(2H,m),6.98-7.06(3H,m),6.36(2H, d,J=1.9Hz),6.06(1H,s),5.91(1H,t,J=5.4Hz),5.41(1H,d,J=5.6Hz),5.30-5.45(1H,m),

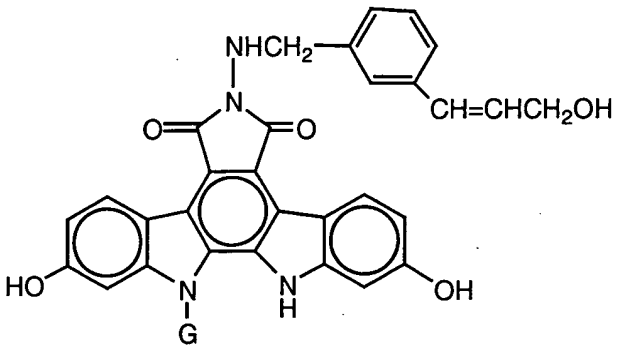
5.20(1H,d,J=4.6Hz),4.87(1H,m),3.94-4.10(4H,m),3.56-3.77(3H,m),3.38-3.43(2H,m)

Example 7

Compound represented by the structural formula

【0046】

【Com. 18】



30 mg of Compound C and 30 mg of 3-(3-hydroxypropenyl)benzylhyrazine trifluoroacetate salt were dissolved in 2 ml of N,N-dimethylformamide, several drops of triethylamine was added, and the mixture was stirred overnight at 80℃. The reaction mixture was concentrated to dryness, and the residue was purified by preparative thin layer chromatography (developing solvent ; acetonitrile: tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1) to obtain 8.2 mg of the compound represented by the above formula.

Rf value: 0.51 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS(m/z):

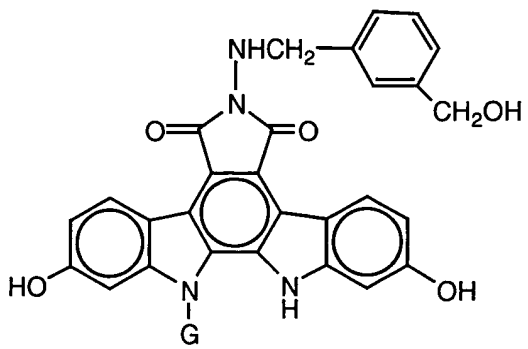
^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.18(1H,s),9.50-10.00(2H,br),8.86(1H,d, J=8.1Hz),8.78(1H,d,J=8.5Hz),7.59(1H,s),7.20-7.40(3H,m),7.16(1H,s),6.97(1H,s),6.73-6.89(2H,m),6.42(1H,d,J=3.6Hz),6.31-6.48(1H,m),6.10(1H,t,J=4.0Hz),5.95(1H,d, J=7.9Hz),5.88(1H,br),5.36(1H,br),5.13(1H,br),4.91(1H,br),4.84(1H,br),4.26(2H,s),4.09(2H,s),3.70-4.10(4H,m),3.41-3.58(2H,m)

Example 8

Compound represented by the structural formula

【0047】

【Com. 19】



45.5 mg of Compound C and 67.2 mg of 3-hydroxymethylbenzylhyrazine trifluoroacetate salt were dissolved in 3 ml of N,N-dimethylformamide, several drops

of aqueous saturated sodium bicarbonate solution was added, and the mixture was stirred overnight at 70℃. The reaction mixture was diluted with methyl ethyl ketone, washed successively with dilute hydrochloric acid, water and saturated saline,. dried and concentrated. The residue was roughly purified by preparative thin layer chromatography (developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1), placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 1.6 mg of the compound represented by the above formula.

Rf value: 0.40(Kieselgel 60F_{254} made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS(m/z): 654 (M^+)

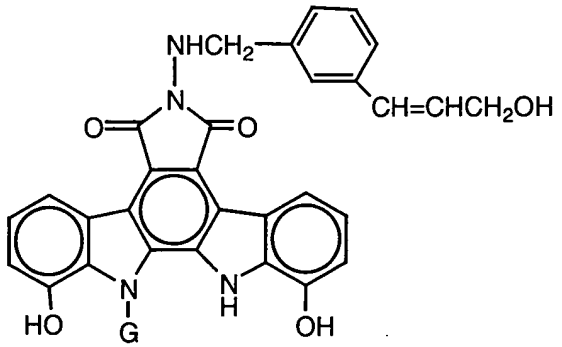
^{1}H-NMR(300MHz,DMSO-d_6,δp pm)11.18(1H,s),8.86(1H,d,J=8.4Hz),8.78(1H,d, J=8.7Hz),7.42(1H,s),7.40(1H,d,J=7.5Hz),7.27(1H,t,J=7.2Hz),7.18(1H,d,J=7.5Hz),7.17 (1H,s),6.98(1H,d,J=1.8Hz),6.81(2H,dt,J=1.8,8.1Hz),6.00(2H,dt,J=1.5,4.8Hz),5.95(1H, d,J=8.7Hz),5.43(1H,br),5.16(2H,br),4.93(1H,br),4.47(2H,s),4.25(1H,d,J=4.8Hz),4.10(1H,br),4.02(1H,d,J=10.8Hz),3.90(2H,m),3.76(1H,m)

Example 9

Compound represented by the structural formula

【0048】

【Com. 20】



30 mg of Compound D and 40 mg of 3-(3-hydroxypropenyl)benzylhyrazine trifluoroacetate salt were dissolved in 1 ml of N,N-dimethylformamide, 0.5 ml of triethylamine was added, and the mixture was stirred at 80℃ for 1.5 hours. The reaction mixture was diluted with a mixed solvent of ethyl acetate/methyl ethyl ketone, washed successively with dilute hydrochloric acid and saturated saline, dried and concentrated. The residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated, and the concentrate was placed again on a Sephadex LH-20 column for chromatography and eluted with ethanol. Fractions containing the desired compound were concentrated to dryness to obtain 7.8 mg of the compound represented by the above formula.

Rf value: 0.48 (Kieselgel 60F_{254} made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

^{1}H-NMR(300MHz,DMSO-d_6,δp pm)10.89(1H,s),10.35(1H,br),9.95(1H,br),8.70(1H, d,J=7.8Hz),8.52(1H,d,J=7.8Hz),7.60(1H,s),6.91-7.40(8H,m),6.53(1H,d,J=16.2Hz), 6.39(1H,td,J=4.6,16.2Hz),6.16(1H,t,J=5.6Hz),5.41(1H,d,J=5.6Hz),5.35(1H,br),5.20(1

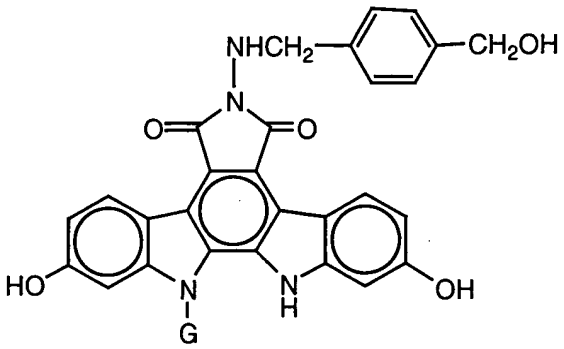
H,d,J=4.9Hz),4.86(1H,t,J=3.6Hz),4.84(1H,t,J=5.6Hz),4.28(2H,s),3.89-4.12(4H,m), 3.30-3.78(4H,m)

Example 10

Compound represented by the structural formula

【0049】

【Com. 21】



100 mg of Compound C and 100 mg of 4-hydroxymethylbenzylhyrazine hydrochloride were dissolved in 5 ml of N,N-dimethylformamide, 0.5 ml of aqueous saturated sodium bicarbonate solution was added, and the mixture was stirred at room temperature for 1 hour and then at 80℃ for 30 minutes. The reaction mixture was diluted with methyl ethyl ketone, washed successively with 2N hydrochloric acid and saturated saline, dried and concentrated. The residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 33 mg of the compound represented by the above formula.

Rf value: 0.47 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; chloroform:methanol:tetrahydrofuran=2:1:1)

FAB-MS (m/z): 655 $(M+H)^+$

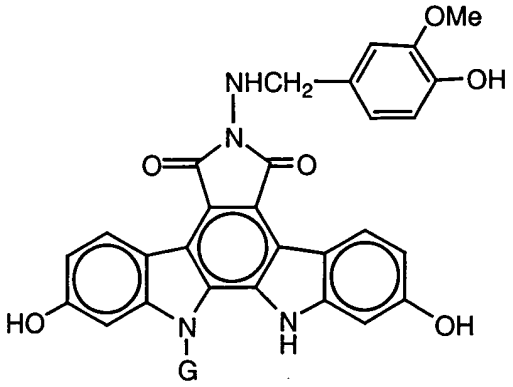
^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.10(1H,br),8.83(1H,d,J=9.3Hz),8.73(1H,d, J=8.4Hz),7.44(2H,d,J=8.4Hz),7.23(2H,d,J=7.8Hz),7.11(1H,s),6.94(1H,s),6.78(2H,dt,J =9.0,2.1Hz),6.02(1H,t,J=4.8Hz),5.92(1H,d,J=8.1Hz),4.80-5.23(2H,br),4.43(2H,s), 4.24(2H,s),4.03(1H,m),3.90(2H,m),3.77(1H,m),3.50(2H,m),3.25-3.42(3H,m)

Example 11

Compound represented by the structural formula

【0050】

【Com. 22】



52 mg of Compound C and 61.4 mg of 3-methoxy-4-hydroxybenzylhyrazine hydrochloride were dissolved in 2 ml of N,N-dimethylformamide, 0.5 ml of aqueous saturated sodium bicarbonate solution was added, and the mixture was stirred at 80℃ for 1 hour. The reaction mixture was concentrated to dryness, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 20 mg of the compound represented by the above formula.

Rf value: 0.33 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; chloroform:methanol:tetrahydrofuran=3:1:1)

FAB-MS (m/z): 655 $(M+H)^+$

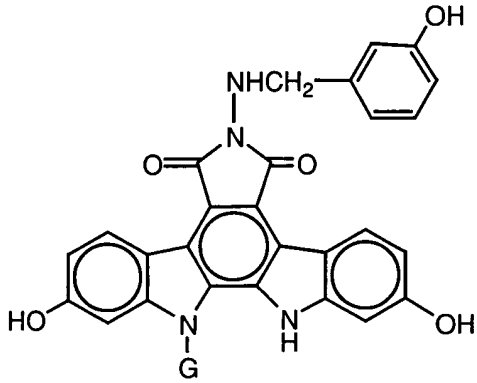
^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.12(1H,s),9.77(1H,s),8.74(1H,s),8.86(1H,s), 8.78(1H,d,J=8.6Hz),8.76(1H,s),7.16(2H,d,J=8.1Hz),6.97(1H,s),6.70-6.85(3H,m),6.64 (1H,d,J=8.5Hz),5.86-6.04(2H,m),5.85(1H,t,J=3.6Hz),5.32(1H,d,J=3.9Hz),5.10(1H,d, J=4.2Hz),4.90(1H,d,J=4.3Hz),4.11-4.21(2H,m),3.86-4.10(4H,m),3.77(3H,m),3.35-3.52(2H,m)

Example 12

Compound represented by the structural formula

【0051】

【Com.23】



40 mg of Compound C and 31 mg of 3-hydroxybenzylhyrazine hydrochloride were dissolved in 2 ml of N,N-dimethylformamide, 0.5 ml of aqueous saturated sodium bicarbonate solution was added, and the mixture was stirred overnight at 80℃. The reaction mixture was diluted with ethyl acetate, washed successively with 2N hydrochloric acid, aqueous saturated sodium bicarbonate solution and saturated saline, dried and concentrated. The residue was placed on a Sephadex LH-20 column for

chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 17.2 mg of the compound represented by the above formula.

Rf value: 0.24 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS (m/z): 641 $(M+H)^+$

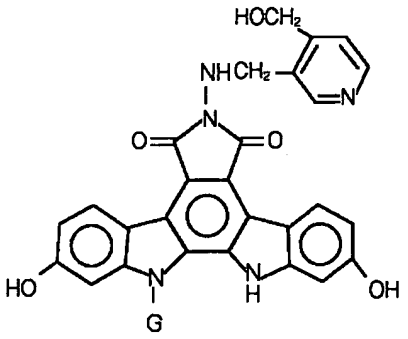
^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.18(1H,s),9.76(1H,s),9.73(1H,s),9.28(1H,s), 8.87(1H,d,J=8.5Hz),8.79(1H,d,J=9.0Hz),7.17(1H,s),7.18(1H,dd,J=7.5,8.0Hz),6.97(1H, d,J=2.3Hz),6.78-6.93(4H,m),6.60(1H,dd,J=1.5,8.0Hz),5.96(2H,m),5.85(1H,m),5.30 (1H,d,J=4.2Hz),5.09(1H,d,J=4.9Hz),4.90(1H,d,J=5.1Hz),4.15(2H,s),3.72-4.05(4H,m) 3.50(2H,m)

Example 13

Compound represented by the structural formula

【0052】

【Com. 24】



43 mg of Compound A and 100 mg of (3-t-butyldimethylsilyloxymethyl)-3-pyridinecarbaldehyde were suspended in 10 ml of methanol, 18 ml of acetic acid was added, and the mixture was stirred overnight at 80℃. The reaction mixture was concentrated, put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was dissolved in 5 ml of a mixed solvent of methanol/tetrahydrofuran (1:1). 5 % palladium-carbon was added and the mixture was stirred at room temperature for 3.5 hours under a hydrogen stream. The reaction mixture was filtered using Celite and the residue was dissolved in 5 ml of tetrahydrofuran. An excess amount of tetrabutylammonium fluoride (1.0 M tetrahydrofuran solution) was added and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated, put on a Sephadex LH-20 column for chromatography, and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 4.3 mg of the compound represented by the above formula.

Rf value: 0.1 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):656$(M+H)^+$

^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.18(1H,s),9.75(1H,s),9.73(1H,s),8.84(1H,d,

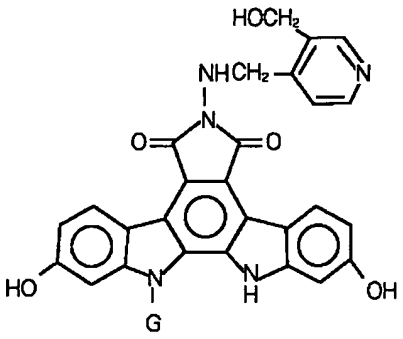
J=8.4Hz),8.77(1H,d,J=8.9Hz),8.42(1H,d,J=4.9Hz),8.39(1H,s),7.48(1H,d,J=4.9Hz),7.17(1H,d,J=1.1Hz),6.97(1H,s),6.78-6.83(2H,m),609(1H,t,J=4.7Hz),5.97(1H,d,J=6.6Hz),5.84(1H,t,J=3.8Hz),5.39(1H,t,J=5.8Hz),5.30(1H,d,J=4.8Hz),5.09(1H,d,J=4.2Hz),4.95(2H,d,J=5.3Hz),4.90(1H,d,J=3.3Hz),4.27(2H,d,J=4.2Hz),3.75-4.03(4H,m),3.47-3.52 (2H,m)

Example 14

Compound represented by the structural formula

【0053】

【Com. 25】



98 mg of Compound A and 92.1 mg of 4-(3-t-butoxymethyl)pyridinecarbaldehyde were dissolved in 5 ml of methanol, 18 ml of acetic acid was added, and the mixture was stirred overnight at 80℃. The reaction mixture was concentrated, and the resulting crystals were washed with chloroform and dissolved in a mixed solvent of methanol/tetrahydrofuran (1:1). 5 % palladium-carbon was added and the mixture was stirred for 3 hours under a hydrogen stream. The reaction mixture was filtered using Celite and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran, tetrabutylammonium fluoride was added, and the mixture was stirred at room temperature for 30 minutes. Water was added, the mixture was extracted with methyl ethyl ketone, and the organic layer was washed with an aqueous saturated sodium chloride solution and concentrated. The concentrate was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 13.5 mg of the compound represented by the above formula.

Rf value: 0.10 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; chloroform: methanol: tetrahydrofuran = 2:2:1)

FAB-MS(m/z):656$(M+H)^+$

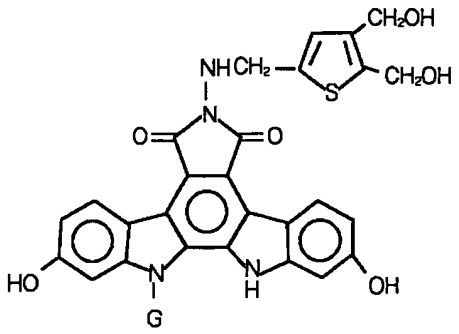
^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.19(1H,s),9.78(1H,s),9.75(1H,s)8.85(1H,d,J=9.1Hz),8.77(1H,d,J=9.1Hz),8.51(1H,s),8.11(1H,d,J=5.1Hz),7.59(1H,d,J=4.6Hz),7.17(1H,d,J=2.1Hz),6.97(1H,d,J=1.8Hz),6.79-6.85(2H,m),6.25(1H,t,J=5.0Hz),5.98(1H,d,J=8.3Hz),5.86(1H,d,J=4.5Hz),5.32(1H,d,J=4.5Hz),5.23(1H,t,J=5.6Hz),5.11(1H,d,J=4.4Hz),4.91(1H,d,J=4.9Hz),4.74(2H,d,J=5.2Hz),4.35(2H,d,J=7.8Hz),3.73-4.05(4H,m),3.43-3.52(2H,m)

Example 15

Compound represented by the structural formula

【0054】

【Com. 26】



50 mg of Compound A and 100 mg of (4,5-t-butyldimethylsilyloxymethyl) thiophene-2-carboxyaldehyde were suspended in 10 ml of anhydrous methanol, 100 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 40 mg of an intermediate compound. This was suspended in 3 ml of methanol, 12 mg of sodium cyanoborohydride and and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was purified by preparative thin layer chromatography (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1) to obtain 26 mg of the compound represented by the above formula.

Rf value: 0.28 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):690(M^+)

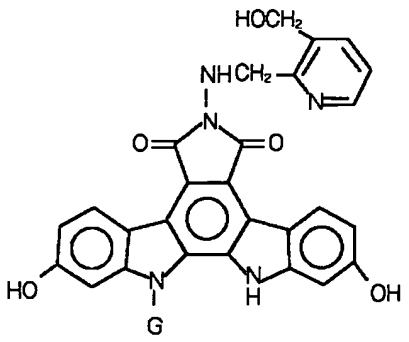
^{1}H-NMR(300MHz,DMSO-d_6,δppm):11.17(1H,s),9.50-10.15(2H,br),8.86(1H,d, J=8.4Hz),8.78(1H,d,J=8.7Hz),7.16(1H,d,J=1.8Hz),6.97(1H,d,J=2.1Hz),6.92(1H,s),6.82(1H,dd,J=1.8,8.7Hz),6.79(1H,dd,J=2.1,8.4Hz),6.04(1H,t,J=5.1Hz),6.04(1H,t.J=5.1Hz),5.96(1H,d,J=8.1Hz),5.88(1H,br),5.35(1H,br),5.28(1H,br),5.15(1H,br),4.93(2H,br),4.53(2H,br),4.73(2H,d,J=4.5Hz),4.30(1H,s),4.00(1H,m),3.91(2H,m),3.77(1H,m),3.52(2H,m)

Example 16

Compound represented by the structural formula

【0055】

【Com. 27】



30 mg of Compound A and 50 mg of 2-(3-t-butyldimethylsilyloxymethyl) pyridinecarbaldehyde were suspended in 6 ml of methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to obtain 40 mg of an intermediate compound. This was dissolved in a mixed solvent of tetrahydrofuran/methanol (2:1), 15 mg of sodium cyanoborohydride and 3 ml of a solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 3 hour. The reaction mixture was concentrated, put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 27 mg of the compound represented by the above formula.

Rf value: 0.12 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):656$(M+H)^+$

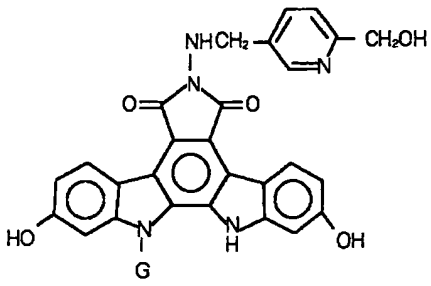
^{1}H-NMR(300MHz,DMSO-d_6 ,δppm):11.18(1H,br),9,77(2H,br,)8,82(1H,d, J=9.0Hz), 8.784(1H,d,J=9.0Hz),8.27(1H,dd,J=1.8,5.1Hz),7.83(1H,d,J=8.1Hz),7.28(1H,dd,J=8.1, 5.1Hz),7.17(1H,d,J=1.8Hz),6.98(1H,d,J=1.8Hz),6.82(1H,dd,J=1.8,9.1Hz),6.79(1H,dd, J=1.8,9.0Hz),6.15(1H,t,J=5.1Hz),5.97(1H,d,J=8.1Hz),5.86(1H,t,J=4.2Hz),5.33(1H,d,J =5.4Hz),5.31(1H,d,J=5.4Hz),5.12(1H,d,J=4.8Hz),4.93(1H,d,J=4.5Hz),4.87(2H,d,J=6.0 Hz),4.36(2H,d,J=5.1Hz),4.03(1H,m),3.91(2H,s),3.79(1H,m),3.51(2H,m)

Example 17

Compound represented by the structural formula

【0056】

【Com. 28】



30 mg of Compound C and 65 mg of (6-hydroxymethyl-3-pyridylmethyl)hydrazine hydrochloride were dissolved in 5 ml of N,N-dimethylformamide, 0.5 ml of triethylamine was added, and the mixture was stirred at 80℃ for 3 hours. 33 mg of (6-hydroxymethyl-3-pyridylmethyl)hydrazine hydrochloride was added and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was concentrated to dryness, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated, and the residue was again put on a Sephadex LH-20 column for chromatography and eluted with ethanol. Fractions containing the desired compound were concentrated to dryness to obtain 7.2 mg of the compound represented by the above formula.

FAB-MS(m/z):656$(M+H)^+$

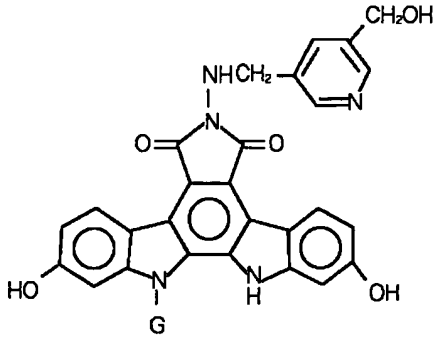
^{1}H-NMR(300MHz,DMSO-d_6,δppm):11.12(1H,br),8.81(1H,d,J=8.7Hz),8.73(1H,d,J=8.7Hz),8.51(1H,s),7.90(1H,d,J=7.9Hz),7.39(1H,d,J=7.9Hz),7.11(1H,s),6.93(1H,s),6.77(2H,t,J=8.7Hz),6.21(1H,t,J=3.8Hz),5.92(1H,d,J=7.9Hz),4.85-5.50(5H,br),4.48(2H,s),4.27(2H,d,J=3.8Hz),3.70-4.05(4H,m),3.45-3.52(2H,m)

Example 18

Compound represented by the structural formula

【0057】

【Com. 29】



12.5 mg of Compound C and 42 mg of (5-hydroxymethyl-3-pyridylmethyl) hydrazine hydrochloride were dissolved in 1 ml of N,N-dimethylformamide, 0.1 ml of triethylamine was added, and the mixture was stirred at 80℃ for 2.5 hours. 0.1 ml of triethylamine was added and the mixture was stirred overnight at 50℃. The reaction mixture was concentrated to dryness, and the residue was put on a Sephadex LH-20

column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated, and the residue was again put on a Sephadex LH-20 column for chromatography and eluted with ethanol. Fractions containing the desired compound were concentrated to dryness to obtain 2.4 mg of the compound represented by the above formula.

Rf value: 0.18 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):656$(M+H)^+$

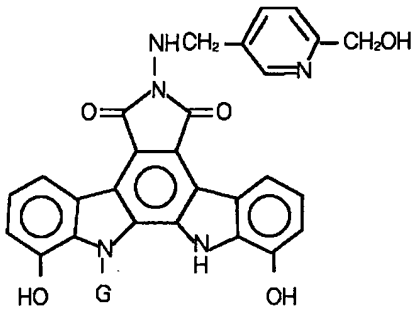
^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.18(1H,br),9.60-10.02(2H,br),8.84(1H,d, J=8.5Hz),8.76(1H,d,J=8.6Hz),8.55(1H,s),8.37(1H,s),7.84(1H,s),7.16(1H,s),7.00(1H,s), 6.75-6.85(2H,m),6.21(1H,t,J=4.7Hz),5.95(1H,d,J=7.8Hz),5.88-5.95(1H,br),5.40-5.48 (1H,br),5.26-5.35(1H,br),5.15-5.25(1H,br),4.90-4.93(1H,br),4.56(2H,d,J=4.7Hz),4.50 (2H, s),3.72-4.05(4H,m),3.45-3.55(2H,m)

Example 19

Compound represented by the structural formula

【0058】

【Com. 30】



30 mg of Compound D and 65 mg of (6-hydroxymethyl-3-pyridylmethyl)hydrazine hydrochloride were dissolved in 5 ml of N,N-dimethylformamide, 0.5 ml of triethylamine was added, and the mixture was stirred at 80℃ for 1.5 hours. The reaction mixture was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 29 mg of the compound represented by the above formula.

FAB-MS(m/z):656$(M+H)^+$

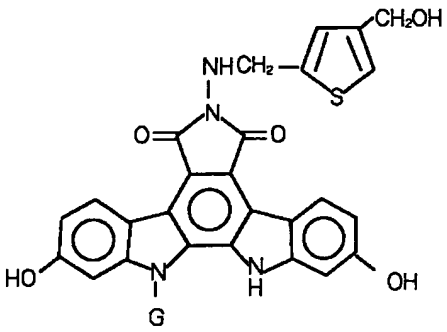
^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):10.89(1H,br),10.36(1H,br),9.97(1H,br),8.67 (1H,d,J=7.9Hz),8.52(1H,d,J=2.2Hz),8.50(1H,d,J=7.9Hz),7.93(1H,dd,J=2.2,8.1Hz),7.4 1(1H,d,J=8.1Hz),7.18(2H,t,J=7.9Hz),7.02(1H,d,J=7.9Hz),7.00(2H,t,J=7.9Hz),6.29(1H, t,J=4.5Hz),5.42(1H,d,J=5.6Hz),5.33(1H,d,J=6.1Hz),5.32(1H,t,J=6.0Hz),5.21(1H,d,J=5 .3Hz),4.82-4.91(1H,br),4.48(2H,d,J=6.0Hz),4.29(2H,d,J=4.5Hz),3.91-4.12(2H,m), 3.52-3.79(3H,m),3.30-3.40(1H,m)

Example 20

Compound represented by the structural formula

【0059】

【Com. 31】



30 mg of Compound B and 152 mg of 4-(t-butyldimethylsilyloxyethyl)thiophene-2-carbaldehyde were suspended in 6 ml of anhydrous methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 31 mg of an intermediate compound. This was suspended in 3 ml of methanol, 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 5 mg of the compound represented by the above formula.

Rf value: 0.43 (made by Merck Co., toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):675$(M)^+$

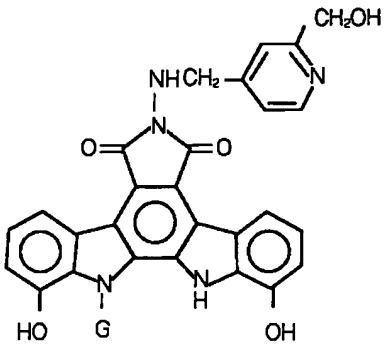
^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.19(1H,s),9.80(2H,br),8.86(1H,d,J=9.0Hz), 8.78(1H,d,J=8.7Hz),7.17(1H,d,J=1.8Hz),7.03(1H,s),6.98(1H,d,J=2.1Hz),6.95(1H,s),6.80(2H,dt,J=2.1,8.7Hz),6.08(1H,t,J=5.1Hz),5.96(1H,d,J=7.8Hz),5.89(1H,br),5.36(1H,br),5.13(1H,br),4.93(1H,br),4.57(1H,br),4.38(2H,d,J=4.2Hz),4.05(2H,m),3.92(2H,s),3.77(1H,m),3.50(5H,m)

Example 21

Compound represented by the structural formula

【0060】

【Com. 32】



17 mg of Compound D and 12 mg of 4-(2-hydroxymethyl-4-pyridylmethyl) hydrazine trifluoroacetate were dissolved in 2 ml of N,N-dimethylformamide, 0.1 ml of triethylamine was added, and the mixture was stirred at 75℃ for 2 hours. Water and ethyl acetate were added to the reaction mixture, and the mixture was extracted three times with water. Sodium chloride was added to the aqueous layer and the mixture was extracted three times with methyl ethyl ketone. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 8 mg of the compound represented by the above formula.

FAB-MS(m/z):656$(M+H)^+$

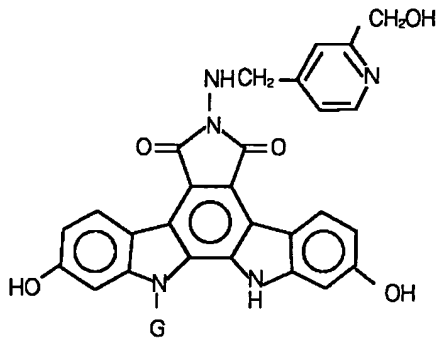
^{1}H-NMR(300MHz,DMSO-d_6 ,δppm):10.90(1H,br),8.66(1H,d,J=7.6Hz),8.50(1H,d, J=7.6Hz),8.41(1H,d,J=5.0Hz),7.57(1H,s),7.48(1H,d,J=5.0Hz),7.17(2H,t,J=7.6Hz),7.07 (1H,d,J=7.6Hz),7.00(1H,d,J=7.6Hz),6.98(1H,t,J=7.6Hz),6.32(1H,t,J=4.8Hz),5.36(1H,t, J=3.7Hz),5.10-5.50(4H,br),4.51(2H,d,J=3.7Hz),4.34(2H,d,J=4.8Hz),3.91-4.12(2H,m), 3.51-3.80(3H,m)

Example 22

Compound represented by the structural formula

【0061】

【Com. 33】



17 mg of Compound C and 12 mg of (2-hydroxymethyl-4-pyridylmethyl)hydrazine

trifluoroacetate were dissolved in 1 ml of N,N-dimethylformamide, 0.1 ml of triethylamine was added, and the mixture was stirred at 80℃ for 3.5 hours. Water and ethyl acetate were added to the reaction mixture, and the mixture was separated into two layers. Sodium chloride was added to the aqueous layer and the mixture was extracted with methyl ethyl ketone. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 4 mg of the compound represented by the above formula.

FAB-MS(m/z):656($M+H^+$)

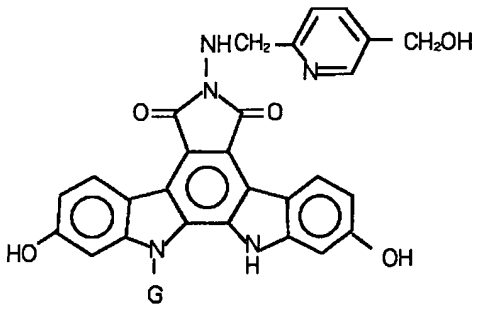
^{1}H-NMR(300MHz,DMSO-d_6,δppm):11.17(1H,br),9.55-10.05(2H,br),8.85(1H,d,J=8.4Hz),8.77(1H,d,J=8.2Hz),8.41(1H,d,J=5.1Hz),7.56(1H,s),7.47(1H,d,J=5.1Hz),7.15(1H,s),6.96(1H,s),6.72-6.85(2H,m),6.26(1H,t,J=4.9Hz),5.94(1H,d,J=8.6Hz),5.80-5.99(1H,br),5.30-5.42(2H,br),5.10-5.20(1H,br),4.85-4.95(1H,br),4.51(2H,d,J=1.8Hz),4.32(2H,d,J=4.5Hz),3.89-4.04(1H,m),3.90(2H,m),3.74-3.78(1H,m),3.50 (2H,m)

Example 23

Compound represented by the structural formula

【0062】

【Com. 34】



14 mg of Compound A and 14.7 mg of 5-t-butyldimethylsilyloxymethylpyridine-2-carbaldehyde were suspended in 2 ml of anhydrous methanol, 8 ml of acetic acid was added, and the mixture was stirred overnight at 80℃. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 15.3 mg of an intermediate compound. 75 mg of sodium cyanoborohydride was suspended in 1 ml of tetrahydrofuran, and 0.55 ml of zinc chloride (1.0 M diethyl ether solution) was added dropwise. A suspension of 15.3 mg of the intermediate compound in 3 ml of tetrahydrofuran was added, and the mixture was stirred at room temperature for 2.5 hours. An aqueous saturated sodium bicarbonate solution was added to the reaction mixture, and the mixture was extracted with methyl ethyl ketone. The organic layer was dried and concentrated, the residue was dissolved in 3 ml of tetrahydrofuran, and an excess amount of tetrabutylammonium fluoride (1 M tetrahydrofuran solution) was added dropwise at 0℃. The mixture was stirred at room temperature for 30 minutes, water was added, and the mixture was extracted with methyl ethyl ketone. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20

column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 4.5 mg of the compound represented by the above formula.

Rf value: 0.1 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; chloroform: methanol: tetrahydrofuran = 3:1:1)

FAB-MS(m/z):656$(M+H)^+$

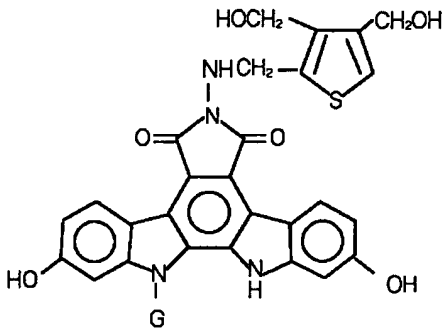
^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.18(1H,s),9.77(2H,br),8.84(1H,d,J=8.5Hz), 8.76(1H,d,J=8.6Hz),8.35(1H,d,J=1.7Hz),7.72(2H,s),7.17(1H,d,J=1.7Hz),6.98(1H,d,J= 1.9Hz),6.78-6.98(2H,m),6.22(1H,t,J=4.6Hz),5.96(1H,d,J=8.9Hz),5.87(1H,br),5.35(1H, br),5.22(1H,t,J=2.0Hz),5.11(1H,br),4.91(1H,br),4.46(2H,d,J=4.2Hz),4.35(2H,d,J=4.6H z),3.73-4.09(4H,m),3.49(2H, s)

Example 24

Compound represented by the structural formula

【0063】

【Com. 35】



30 mg of Compound A and 30 mg of 3,4-bis-(t-butyldimethylsilyloxymethyl) thiophene-2-carbaldehyde were suspended in 6 ml of anhydrous methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 31 mg of an intermediate compound. This was suspended in 5 ml of methanol, 10 mg of sodium cyanoborohydride and 100 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, and washed with water and an aqueous saturated sodium chloride solution. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 25 mg of the compound represented by the above formula.

Rf value: 0.30 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):691$(M+H)^+$

^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.19(1H,s),9.79(1H,s),9.76(1H,s),8.86(1H,

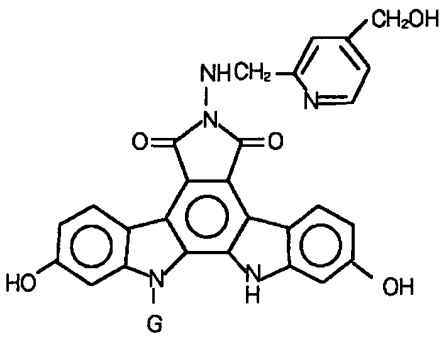
d,J=8.4Hz),8.78(1H,d,J=8.7Hz),7.18(1H,d,J=1.8Hz),7.15(1H,s),6.98(1H,d,J=2.1Hz),6.82(2H,dt,J=8.7,1.8Hz),6.04(1H,t,J=5.4Hz),5.97(1H,d,J=8.1Hz),5.86(1H,t,J=3.6Hz),5.33(1H,d,J=4.2Hz),5.12(1H,d,J=4.2Hz),5.01(1H,t,J=6.0Hz),4.93(1H,d,J=4.8Hz),4.85(1H,t,J=5.7Hz),4.52(2H,d,J=5.7Hz),4.70(2H,d,J=5.7Hz),4.40(2H,d,J=4.8Hz),4.01(1H,m),3.92(2H,m),3.77(1H,m),3.50(2H,m)

Example 25

Compound represented by the structural formula

【0064】

【Com. 36】



18 mg of Compound A and 7 mg of 4-hydroxymethylpyridine-2-carbaldehyde were suspended in 2 ml of anhydrous methanol, several drops of acetic acid were added, and the mixture was stirred at 80℃ for 1.5 hours. The reaction mixture was concentrated to dryness, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 22 mg of an intermediate compound. 90 mg of sodium cyanoborohydride was suspended in 1 ml of tetrahydrofuran, and 0.66 ml of zinc chloride (1.0 M diethyl ether solution) was added dropwise. A suspension of 22 mg of the intermediate compound in 3 ml of tetrahydrofuran was added, and the mixture was stirred at room temperature for 2.5 hours. Water was added to the reaction mixture, and the mixture was made weakly alkaline with an aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 11 mg of the compound represented by the above formula.

FAB-MS(m/z):656$(M+H)^+$

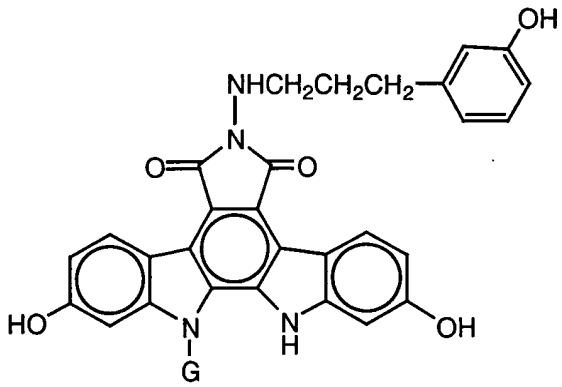
^{1}H-NMR(300MHz,DMSO-d_6 ,δppm):11.21(1H,s),9.80(1H,s),9.77(1H,s),8.86(1H,d,J=8.6Hz),8.78(1H,d,J=8.1Hz),7.82-7.95(1H,m),7.68-7.75(1H,m),7.33-7.43(1H,m),7.19(1H,s),7.00(1H,s),6.78-6.89(2H,m),6.22(1H,t,J=4.5Hz),5.97(1H,d,J=7.9Hz),5.86(1H,t,J=3.8Hz),5.33(1H,d,J=4.2Hz),5.29(1H,t,J=5.9Hz),5.11(1H,d,J=5.0Hz),4.91(1H,d,J=4.1Hz),4.42(2H,d,J=5.5Hz),4.33(2H,d,J=1.6Hz),3.99-4.09(1H,m),3.91(2H,m),3.72-3.80(1H,m),3.50(2H,m)

Example 26

Compound represented by the structural formula

【0065】

【Com. 37】



20 mg of Compound A and 20 mg of 3-(3-t-butyldimethylsilyloxyphenyl)propanal were suspended in 4 ml of anhydrous methanol, 20 ml of acetic acid was added, and the mixture was stirred at 80℃ for 8 hours. The reaction mixture was concentrated, and the concentrate was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 14 mg of an intermediate compound. This was suspended in 5 ml of methanol, 7.5 mg of sodium cyanoborohydride and 0.5 ml of a 10 % solution of hydrochloric acid in methanol were added, the mixture was stirred at room temperature for 2 hours, 0.5 ml of 2N hydrochloric acid was added, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed successively with water and saturated saline. The organic layer was dried and concentrated, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 12 mg of the compound represented by the above formula.

Rf value: 0.36 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS (m/z): 669 $(M+H)^+$

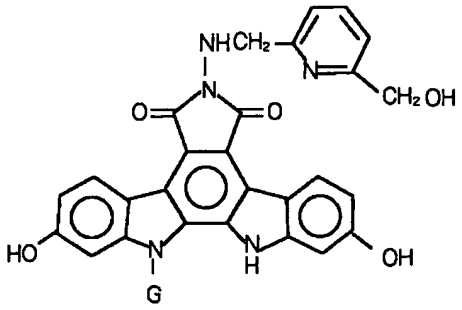
^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.18(1H,s),9.65(3H,br),8.87(1H,d,J=8.1Hz), 8.79(1H,d,J=8.1Hz),7.17(1H,d,J=1.7Hz),7.02(1H,t,J=8.1Hz),6.98(1H,d,J=1.7Hz),6.81(2H,dt,J=1.7,5.7Hz),6.64(1H,d,J=8.1Hz),6.62(1H,s),6.57(1H,dd,J=1.8,8.1Hz),5.96(1H, d,J=8.1Hz),5.87(1H,br),5.74(1H,t,J=4.8Hz),5.35(1H,br),5.12(1H,br),4.92(1H,br),4.02(1H,d,J=10.8Hz),3.91(2H,m),3.79(1H,d,J=9.9Hz),3.51(2H,d,J=7.5Hz),3.02(2H,m),2.65 (2H,t,J=7.2Hz),1.72(2H,t,J=8.1Hz)

Example 27

Compound represented by the structural formula

【0066】

【Com. 38】



15 mg of Compound A and 6.9 mg of 6-hydroxymethylpyridine-2-carbaldehyde were suspended in 1 ml of anhydrous methanol, several drops of acetic acid were added, and the mixture was stirred at 80℃ for 5 hours. The reaction mixture was concentrated to dryness, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 5.2 mg of an intermediate compound. 68 mg of sodium cyanoborohydride was suspended in 2 ml of tetrahydrofuran, and 0.5 ml of zinc chloride (1.0 M diethyl ether solution) was added dropwise. A suspension of 5.2 mg of the intermediate compound in 1 ml of tetrahydrofuran was added, and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was made weakly alkaline with an aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 2.0 mg of the compound represented by the above formula.

Rf value: 0.29 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):656($M+H^+$)

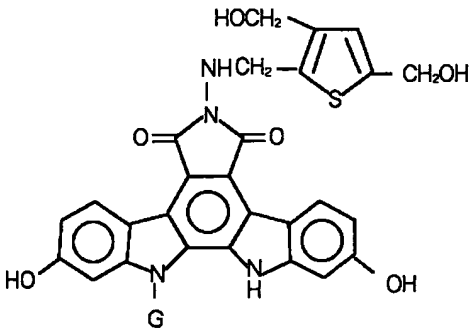
^{1}H-NMR(300MHz,DMSO-d_6 ,δppm):11.21(1H,s),9.80(1H,s),9.77(1H,s),8.86(1H,d, J=8.6Hz),8.78(1H,d,J=8.1Hz),7.82-7.95(1H,m),7.68-7.75(1H,m),7.33-7.43(1H,m), 7.19(1H,s),7.00(1H,s),6.78-6.89(2H,m),6.22(1H,t,J=4.5Hz),5.97(1H,d,J=7.9Hz),5.86 (1H,t,J=3.8Hz),5.33(1H,d,J=4.2Hz),5.29(1H,t,J=5.9Hz),5.11(1H,d,J=5.0Hz),4.91(1H,d ,J=4.1Hz),4.42(2H,d,J=5.5Hz),4.33(2H,d,J=1.6Hz),3.99-4.09(1H,m),3.91(2H,m),3.72-3.80(1H,m),3.50(2H,m)

Example 28

Compound represented by the structural formula

【0067】

【Com. 39】



40 mg of Compound A and 60 mg of 3,5-bis-(t-butyldimethylsilyloxymethyl) thiophene-2-carbaldehyde were suspended in 8 ml of anhydrous methanol, 40 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 46 mg of an intermediate compound. This was suspended in 5 ml of methanol, 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, and washed with water and an aqueous saturated sodium chloride solution. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 36 mg of the compound represented by the above formula.

Rf value: 0.24 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):690$(M)^+$

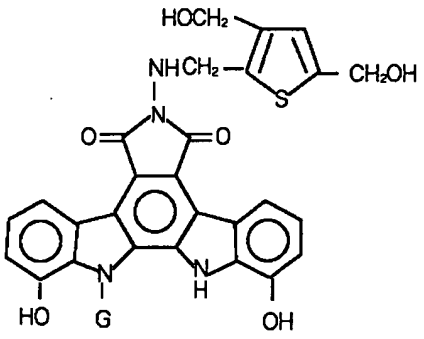
^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.19(1H,s),9.79(1H,s),9.76(1H,s),8.86(1H,d, J=8.4Hz),8.78(1H,d,J=8.4Hz),7.18(1H,d,J=1.8Hz),6.98(1H,d,J=1.8Hz),6.83(1H,s),6.82(2H,dt,J=1.8,8.4Hz),5.99(1H,t,J=4.8Hz),5.97(1H,d,J=9.0Hz),5.87(1H,t,J=4.2Hz),5.35(1H,t,J=5.4Hz),5.33(1H,d,J=4.8Hz),5.12(1H,d,J=5.1Hz),4.96(1H,d,J=5.7Hz),4.94(1H,d,J=5.4Hz),4.49(4H,t,J=6.6Hz),4.34(2H,d,J=4.8Hz),4.03(1H,m),3.92(2H,m),3.77(1H,m),3.50(2H,m)

Example 29

Compound represented by the structural formula

【0068】

【Com. 40】



50 mg of Compound B and 60 mg of 3,5-bis-(t-butyldimethylsilyloxymethyl) thiophene-2-carbaldehyde were dissolved in 12 ml of anhydrous methanol/N,N-dimethylformamide (5:1), 50 ml of acetic acid was added, and the mixture was stirred overnight at 80℃. The reaction mixture was diluted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried, and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was dissolved in 6 ml of a mixed solvent of tetrahydrofuran/methanol (2:1). 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, and washed with an aqueous saturated sodium bicarbonate solution and an aqueous saturated sodium chloride solution. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 37 mg of the compound represented by the above formula.

Rf value: 0.31 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):690$(M)^+$

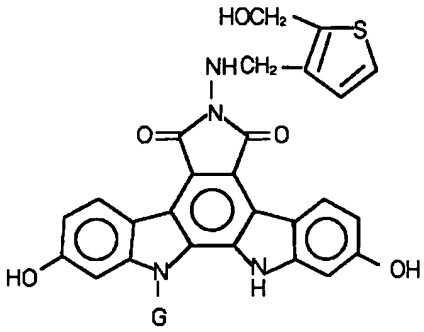
^{1}H-NMR(300MHz,DMSO-d_6, δppm):10.90(1H,s),10.37(1H,br),9.98(1H,br),8.69(1H, d,J=8.4Hz),8.52(1H,d,J=8.4Hz),7.19(2H,dt,J=1.5,8.4Hz),7.05(1H,d,J=8.6Hz),7.01(2H, t,J=8.4Hz),6.83(1H,s),6.04(1H,t,J=4.8Hz),5.42(1H,d,J=5.7Hz),5.35(2H,t,J=6.0Hz),5.2 1(1H,d,J=5.4Hz),4.95(1H,t,J=6.0Hz),4.91(1H,br),4.50(4H,t,J=5.7Hz),4.36(2H,d,J=5.4 Hz),4.00(2H,m),3.73(1H,m),3.62(2H,m),3.40(1H,m)

Example 30

Compound represented by the structural formula

【0069】

【Com. 41】



20 mg of Compound A and 20 mg of 2-hydroxymethylthiophene-3-carbaldehyde were dissolved in 4 ml of anhydrous methanol, 20 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was dissolved in 3 ml of a mixed solvent of tetrahydrofuran/methanol (2:1). 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 16 mg of the compound represented by the above formula.

Rf value: 0.49 (Kieselgel 60F_{254} made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):660$(M)^+$

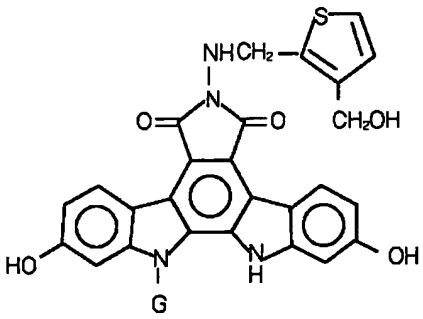
^{1}H-NMR(300MHz,DMSO-d_6 ,δp p m):11.18(1H,s),9.79(1H,s),9.75(1H,s),8.86(1H, d,J=8.4Hz),8.78(1H,d,J=8.4Hz),7.30(1H,d,J=4.8Hz),7.17(1H,d,J=2.1Hz),7.09(1H,d,J= 5.4Hz),6.98(1H,d,J=2.1Hz),6.82(1H,dd,J=2.1,8.4Hz),6.80(1H,dd,J=2.1,8.4Hz),5.97(1 H,d,J=8.1Hz),5.92(1H,t,J=5.1Hz),5.86(1H,t,J=3.9Hz),5.37(1H,d,J=5.7Hz),5.33(1H,d,J =4.5Hz),5.12(1H,d,J=4.8Hz),4.93(1H,d,J=4.8Hz),4.76(2H,d,J=5.7Hz),4.20(2H,d,J=5.1 Hz),4.00(1H,m),3.91(2H,s),3.77(1H,m),3.50(2H,m)

Example 31

Compound represented by the structural formula

【0070】

【Com. 42】



30 mg of Compound A and 30 mg of 3-t-butyldimethylsilyloxymethylthiophene-2-carbaldehyde were dissolved in 5 ml of anhydrous methanol, 30 ml of acetic acid was added, and the mixture was stirred 80℃ for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was suspended in 3 ml of methanol. 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 24 mg of the compound represented by the above formula.

Rf value: 0.40 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):660$(M)^+$

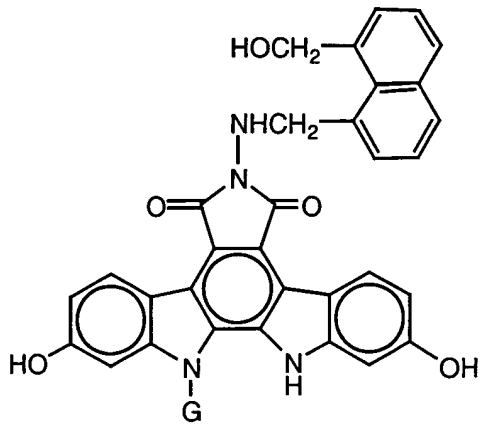
^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.19(1H,s),9.78(1H,s),9.75(1H,s),8.85(1H,d, J=8.7Hz),8.78(1H,d,J=9.0Hz),7.31(1H,d,J=4.8Hz),7.18(1H,d,J=1.8Hz),6.99(1H,d,J=4.8Hz),6.97(1H,d,J=1.8Hz),6.81(2H,dd,J=1.8,9.0Hz),6.06(1H,t,J=4.8Hz),5.97(1H,d,J=8.7Hz),5.86(1H,t,J=3.9Hz),5.33(1H,d,J=4.5Hz),5.12(1H,d,J=4.5Hz),4.99(1H,t,J=5.4Hz), 4.93(1H,d,J=5.1Hz),4.53(2H,d,J=5.7Hz),4.38(2H,d,J=4.8Hz),4.02(1H,m),3.91(2H,m), 3.77(1H,m),3.50(2H,m)

Example 32

Compound represented by the structural formula

【0071】

【Com. 43】



35 mg of Compound A and 60 mg of 8-t-butyldimethylsilyloxymethyl-1-naphthoaldehyde were suspended in 2 ml of methanol, everal drops of acetic acid was added, and the mixture was stirred at 60℃ for 2 hours. The reaction mixture was concentrated, and the resulting solid was washed with chloroform to obtain 32.5 mg of an intermediate compound. 68 mg of sodium cyanoborohydride was suspended in 3 ml of tetrahydrofuran, and 0.5 ml of zinc chloride (1.0 M diethyl ether solution) was added dropwise. A suspension of 32.5 mg of the intermediate compound in 2 ml of tetrahydrofuran was added thereto, and the mixture was stirred at room temperature for 2 hours, saturated saline was added, and the mixture was extracted with a mixed solvent of ethyl acetate/methyl ethyl ketone. The organic layer was dried and concentrated, the residue was dissolved in 1.5 ml of tetrahydrofuran, and 0.5 ml of tetrabutylammonium fluoride was added. The mixture was stirred at room temperature for 1.5 hours, diluted with a mixed solvent of ethyl acetate/methyl ethyl ketone, and washed successively with water and saturated saline. The organic layer was dried and concentrated, and the concentrate was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 3.3 mg of the compound represented by the above formula.

FAB-MS (m/z): 705 $(M+H)^+$

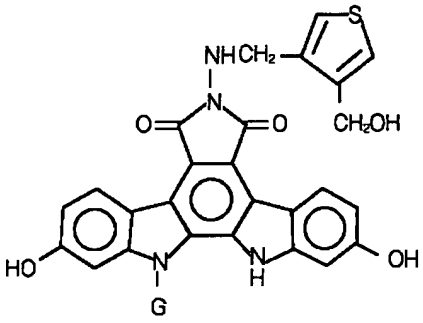
^{1}H-NMR (300MHz,DMSO-d_6,δppm)11.16(1H,s),8.84(1H,d,J=7.9Hz),8.76(1H,d,J=7.9Hz),7.87(2H,d,J=7.4Hz),7.68(1H,d,J=7.4Hz),7.58(1H,d,J=7.4Hz),7.49(1H,d,J=7.4Hz),7.39(1H,t,J=7.4Hz),7.15(1H,s),6.97(1H,s),6.80(2H,t,J=7.9Hz),5.86-6.00(3H,m),5.42(2H,s),4.85(2H,d,J=4.2Hz),4.80-5.50(4H,br),3.72-4.05(4H,m),3.45-3.59(2H,m)

Example 33

Compound represented by the structural formula

【0072】

【Com. 44】



30 mg of Compound A and 30 mg of 4-t-butyldimethylsilyloxythiophene-3-carbaldehyde were suspended in 6 ml of methanol, 30 ml of acetic acid was added, and the mixture was stirred 80℃ for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was dissolved in 5 ml of a mixed slovent of tetrahydrofuran/methanol (2:1). 20 mg of sodium cyanoborohydride and 200 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 15 mg of the compound represented by the above formula.

Rf value: 0.47 (Kieselgel 60F_{254} made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):661$(M+H)^+$

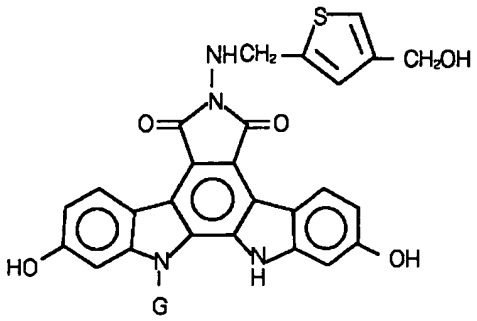
^{1}H-NMR(300MHz,DMSO-d_6 ,δp p m):11.19(1H,s),9.79(1H,s),9.76(1H,s),8.86(1H,d, J=8.7Hz),8.78(1H,d,J=8.7Hz),7.43(1H,d,J=3.3Hz),7.30(1H,d,J=3.6Hz),7.17(1H,d,J=2. 1Hz),6.98(1H,d,J=2.1Hz),6.83(1H,dd,J=2.1,8.7Hz),6.81(1H,dd,J=2.1,8.7Hz),6.04(1H,t ,J=5.1Hz),5.97(1H,d,J=9.0Hz),5.87(1H,t,J=3.6Hz),5.34(1H,d,J=3.9Hz),5.12(1H,d,J=5. 1Hz),5.10(1H,t,J=5.1Hz),4.92(1H,d,J=4.5Hz),4.67(2H,d,J=5.4Hz),4.23(2H,d,J=4.2Hz) ,4.01(1H,m),3.92(2H,s),3.77(1H,m),3.50(2H,m)

Example 34

Compound represented by the structural formula

【0073】

【Com. 45】



38 mg of Compound A and 25 mg of 4-hydroxymethylthiophene-2-carbaldehyde were suspended in 7 ml of anhydrous methanol, 45 ml of acetic acid was added, and the mixture was stirred at 80℃ for 7 hours. The reaction mixture was concentrated under reduced pressure, and 38 mg of crystals obtained by filtration from methanol/chloroform. The crystals were dissolved in 10 ml of tetrahydrofuran/methanol (4:1), 13 mg of sodium cyanoborohydride and 0.5 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with an aqueous saturated sodium chloride solution, dried and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 21.7 mg of the compound represented by the above formula.

Rf value: 0.24 (Kieselgel 60F_{254} made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):660(M^+)

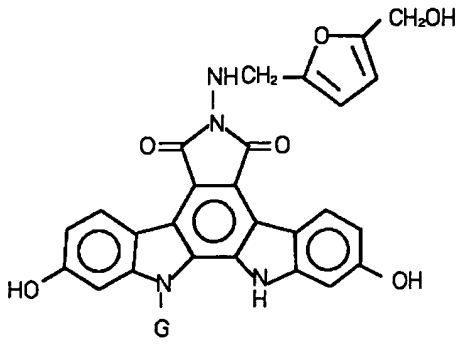
^{1}H-NMR(300MHz,DMSO-d_6,δppm):11.19(1H,s),9.77(2H,br),8.86(1H,d,J=8.6Hz),8.78(1H,d,J=8.6Hz),7.17(1H,s),7.14(1H,d,J=1.8Hz),6.98(2H,m),6.81(2H,dt,J=1.8,6.9Hz),6.12(1H,t,J=5.1Hz),5.97(1H,d,J=8.1Hz),5.87(1H,s),5.35(1H,d,J=1.8Hz),5.13(1H,d,J=2.4Hz),5.01(1H,t,J=5.4Hz),4.93(1H,d,J=3.6Hz),4.40(2H,d,J=4.5Hz),4.34(2H,d,J=4.8Hz),4.00(1H,dd,J=2.1,11.6Hz),3.91(2H,s),3.79(1H,m),3.51(2H,br)

Example 35

Compound represented by the structural formula

【0074】

【Com. 46】



107 mg of Compound A and 126 mg of 5-hydroxymethylfurfural were suspended in 2 ml of methanol, several drops of acetic acid were added, and the mixture was stirred overnight at 80℃. The reaction mixture was concentrated and the obtained solid was washed with chloroform. The solid was dissolved in 5 ml of a mixed solvent of methanol/tetrahydrofuran (1:2), 62.8 mg of sodium cyanoborohydride and 5 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with a mixed slovent of ethyl acetate/methyl ethyl ketone, and washed with water and an aqueous saturated sodium chloride solution. The organic layer was dried, concentrated, put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 103 mg of the compound represented by the above formula.

FAB-MS(m/z):644$(M)^+$

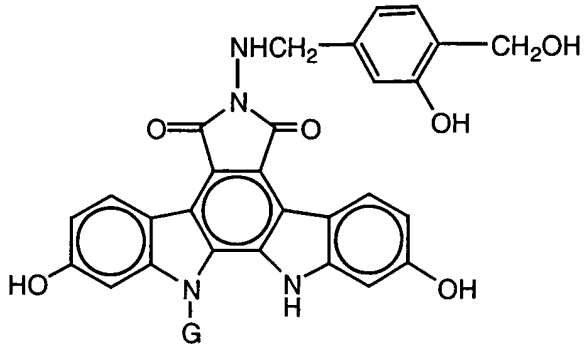
^{1}H-NMR(300MHz,DMSO-d_6 ,δppm):11.19(1H,s),9.77(2H,br),8.85(1H,d,J=8.5Hz), 8.77(1H,d,J=8.6Hz),7.18(1H,d,J=2.1Hz),6.98(1H,d,J=1.7Hz),6.75-6.86(2H,m),6.31 (1H,d,J=3.1Hz),6.15(1H,d,J=3.1Hz),6.03(1H,t,J=4.7Hz),5.97(1H,d,J=8.3Hz),5.87(1H,t ,J=3.6Hz),5.34(1H,d,J=3.9Hz),5.08-5.15(2H,m),4.93(1H,d,J=4.5Hz),4.28(2H,d, J=5.6Hz),4.20(2H,d,J=4.7Hz),3.72-4.05(4H,m),3.45-3.55(2H,m)

Example 36

Compound represented by the structural formula

【0075】

【Com. 47】



39 mg of Compound A and 33 mg of 3-hydroxy-4-hydroxymethylbenzaldehyde were suspended in 8 ml of methanol, 150μl of acetic acid was added, and the mixture was stirred at room temperature over a period of three nights. The reaction mixture was

filtered, and the resulting solid was washed with chloroform. The solid was dissolved in 5 ml of a mixed solvent of methanol/tetrahydrofuran (1:2), 9 mg of sodium cyanoborohydride and several drops of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated to dryness, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 3.5 mg of the compound represented by the above formula.

FAB-MS (m/z): 670 (M^+)

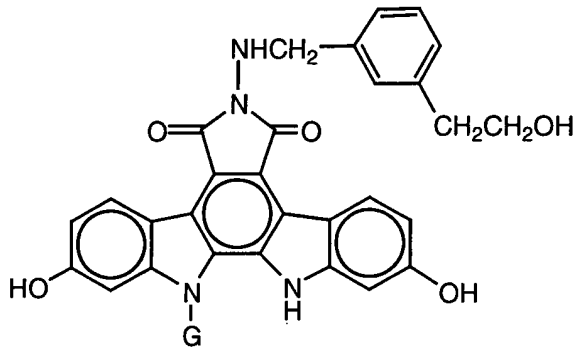
^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.18(1H,s),9.77(1H,s),9.76(1H,s),9.28(1H,br), 8.87(1H,d,J=8.5Hz),8.78(1H,d,J=8.5Hz),7.18(1H,d,J=7.9Hz),7.17(1H,s),6.97(1H,d,J= 2.0Hz),6.77-6.93(4H,m),5.96(1H,d,J=8.2Hz),5.92(1H,t,J=5.0Hz),5.86(1H,t,J=3.2Hz), 5.33(1H,d,J=4.3Hz),5.12(1H,d,J=4.6Hz),4.92(1H,d,J=5.0Hz),5.83(1H,br),4.41(2H,d,J =3.2Hz),4.14(2H,d,J=5.0Hz),4.00(1H,m),3.90(2H,m),3.78(1H,m),3.50(2H,m)

Example 37

Compound represented by the structural formula

【0076】

【Com. 48】

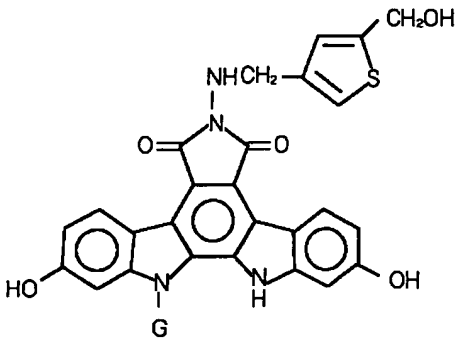


30 mg of Compound A and 24.9 mg of 3-(2-hydroxyethyl)benzaldehyde were suspended in 1 ml of methanol, several drops of acetic acid was added, and the mixture was stirred at 80℃ for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was washed with chloroform. This was suspended in 2 ml of methanol, 9.0 mg of sodium cyanoborohydride and several drops of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated to dryness, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 20.7 mg of the compound represented by the above formula.

FAB-MS (m/z): 669 $(M+H)^+$

^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.18(1H,s),9.78(1H,s),9.75(1H,s),8.87 (1H,d,J=8.5Hz),8.79(1H,d,J=8.6Hz),7.36(1H,s),7.32(1H,d,J=7.6Hz),7.15-7.25 (2H,m), 7.07(1H,d,J=7.6Hz),6.97(1H,d,J=2.0Hz),6.75-6.85(2H,m),6.02(1H,d,J=5.2Hz),5.96 (1H,d,J=8.2Hz),5.86(1H,t,J=3.3Hz),5.33(1H,d,J=4.3Hz),5.11(1H,d,J=4.9Hz),4.90(1H, d,J=5.4Hz),4.61(1H,t,J=5.3Hz),4.23(2H,d,J=4.5Hz),3.72-4.05(4H,m),3.45-3.60(4H,m), 2.69(2H,t,J=7.3Hz)

Example 38
Compound represented by the structural formula
【0077】
【Com. 49】



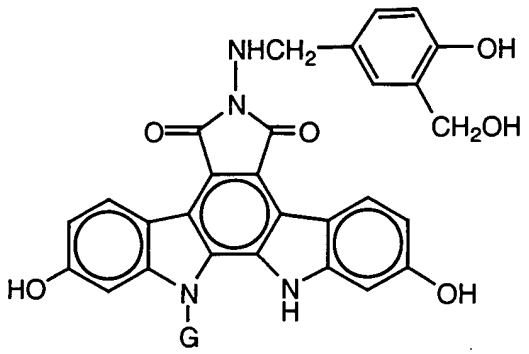
40 mg of Compound A and 40 mg of 5-hydroxymethylthiophene-3-carbaldehyde were suspended in 8 ml of methanol, 40 ml of acetic acid was added, and the mixture was stirred at 80℃ for 3 hours. The reaction mixture was cooled to room temperature, chloroform was added, and the resulting powder was obtained by filtration. This was suspended in 5 ml of methanol, 20 mg of sodium cyanoborohydride and 200 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with a mixed slovent of ethyl acetate/methyl ethyl ketone, washed with water and an aqueous saturated sodium chloride solution, dried, and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 21 mg of the compound represented by the above formula.

Rf value: 0.29 (Kieselgel 60F_{254} made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):660(M^+)

^{1}H-NMR(300MHz,DMSO-d_6 ,δppm):11.19(1H,s),9.80(2H,br),8.86(1H,d,J=9.0Hz), 8.79(1H,d,J=8.7Hz),7.34(1H,s),7.17(1H,d,J=1.5Hz),7.04(1H,s),6.97(1H,d,J=1.5Hz),6. 82(1H,dd,J=1.5,9.0Hz),6.80(1H,dd,J=8.7,1.5Hz),5.97(2H,t,J=5.1Hz),5.87(1H,br),5.40(1H,t,J=6.0Hz),5.35(1H,br),5.13(1H,s),4.91(1H,d,J=3.9Hz),4.57(2H,d,J=4.2Hz),4.20(2 H,d,J=4.8Hz),3.88-4.10(3H,m),3.78(1H,m),3.50(2H,m)

Example 39
Compound represented by the structural formula
【0078】
【Com. 50】



38 mg of Compound A and 91 mg of 3-hydroxymethyl-4-hydroxybenzaldehyde were dissolved in 2 ml of N,N-dimethylformamide, three drops of acetic acid was added, and the mixture was stirred at 80℃ for 3 hour. The reaction mixture was concentrated under reduced pressure, and the residue was washed with chloroform. This was suspended in 3 ml of methanol, 40 mg of sodium cyanoborohydride and several drops of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 8.9 mg of the compound represented by the above formula.

Rf value: 0.15 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS (m/z):

^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.19(1H,s),9.75(1H,br),9.74(1H,br),9.23(1H,br),8.87(1H,d,J=8.6Hz),8.79(1H,d,J=8.6Hz),7.37(1H,s),7.12-7.20(2H,m),6.98(1H,d,J=2.1Hz),6.75-6.85(2H,m),6.70(1H,d,J=8.3Hz),5.97(1H,d,J=8.3Hz),5.86(1H,t,J=4.4Hz),5.76(1H,t,J=5.3Hz),5.33(1H,d,J=4.4Hz),5.10(1H,d,J=3.4Hz),4.89-4.98(2H,m),4.44(2H,d,J=4.5Hz),3.72-4.15(6H,m),3.48-3.55(2H,m)

【0079】

【Effect of the Invention】

The compounds of the invention have excellent antitumor effect, and are useful as antitumor agents in the field of medicine.

【0080】

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